Need For High Quality Plasma Derivatives

Donna DiMichele, M
FDA Workshop on Plasma Standard
August 31, 200

Plasma Standards

The Global View

National

- NHF
- MASAC
- BSWG

International

Plasma Standards

Message

- Preserving intent to produce as well as optimizing recovery of clotting factor proteins remain essential responsibilities of the plasma collectors / fractionators, given the national and global needs of the coagulation disorders community.
- National and international harmonization of plasma collection, storage and processing standards may provide the most cost-effective way for stakeholders to fulfill the collective global responsibility to produce safe, effective and affordable product in adequate supply.
- The goal of “harmonization” would be that of equivalence rather than uniformity of process / outcome.

Plasma Standards

Source vs. Recovered Plasma: Characteristics with Implications for IGIV

- **Efficacy**
  - Antibody titers and biologic potency
- **Safety**
  - Record keeping, feasibility and speed of look back, sample / specimen retention
  - Adverse Event Rates
  - Impact of repeat donors receiving repeat testing and education
  - Impact of donation processing, plasma hold and pooling parameters
  - Supply limitations

Plasma Standards

Message

The intent of this presentation is not to:

- Enter the debate on specific regulatory standards for plasma intended for fractionation
  - collection method (time to freezing)
  - storage (freezing temperature)
  - manufacturing process
- Discuss the scientific basis for maximizing yield of labile non-labile clotting factors

Plasma Standards

Demand for PD products

	US	World*	
PD FVIII requirement (% of total) (approx # units)	30% 4.2 x 10^8	58% 1.04 x 10^9	#
PD FIX requirement (% of total) (approx # units)	25%^ 6.5 x 10^7	58% 1.35 x 10^8	#
PD Bypass agent requirement (inhibitors) (% of total)	(est) 25%^	(est) 33%^	
PD product requirement for vWd, RBD's (% of total)	(est) > 95%	(est) > 95%	

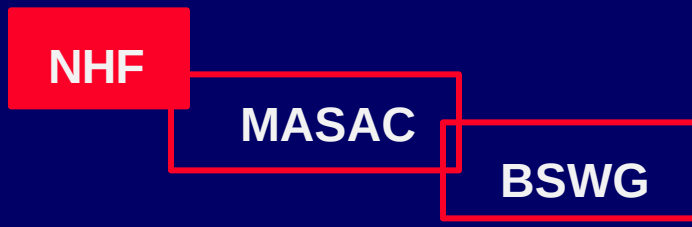
* 75% of need unmet; death from bleeding, HIV, HC (WFH Global Survey, 2003)

% is for combined FVIII / IX global consumption

^ MRB (2003, 2002 figures)

lasma Standards

lational Hemophilia Foundation



Advocacy of recombinant replacement therapy in the US
MASAC Recommendation # 106 (November 2000)

The recombinant factor VIII products (recombinant factor IX product) . . . are (is) the safest . . . with respect to viral transmission and should be considered the treatment of choice for individuals with hemophilia A (hemophilia B)

Plasma Standards

Recombinant Debate Rages

The relative merits (safety / efficacy) of recombinant and plasma-derived products continue to be hotly debated relative to:

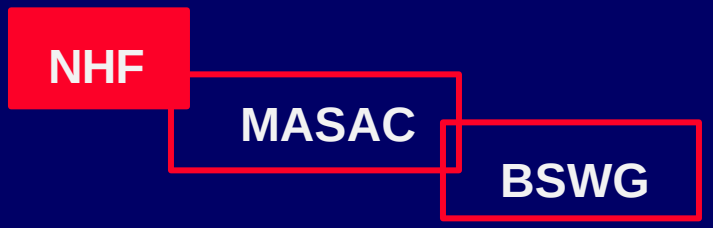
- **inhibitor development**
  (Rothschild et al – JTH 2003; Abstract OC215)
  (Aledort / Lusher – JTH 2004; 2:861 – 865)

- **inhibitor therapy**
  (Ongoing FENOC Study: Berntorp, Astermark et al)
  (WFH Symposium, Thailand October 2004)

- **viral transmission?**

Plasma Standards

National Hemophilia Foundation

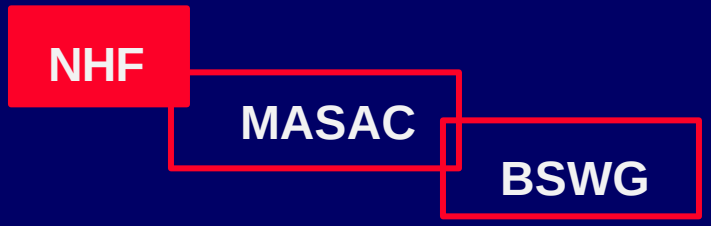


Long history of supporting FDA regulation in the area of plasm
tandards (NHF report language to Congress 2003).

Blood Safety – The Committee is aware that several standards urrently are followed regarding the collection of recovered and ource plasma from blood and encourages FDA to work with all takeholders and collectors of blood and plasma to ensure the quivalence of these standards in safeguarding the nation's lood supply.

Plasma Standards

National Hemophilia Foundation



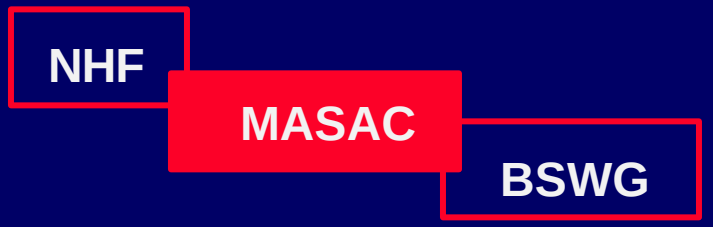
Presentation to the NA PPTA planning meeting (M Skinner, 4/04

Future (Continuing) Role of Plasma-Derived Products in the United States

- ***Rare bleeding disorders***
- ***When recombinant is not an option***
- ***Patient preference***
- ***Supply "backstop"***
- ***Reimbursement / cost dictates***

Plasma Standards

MASAC*

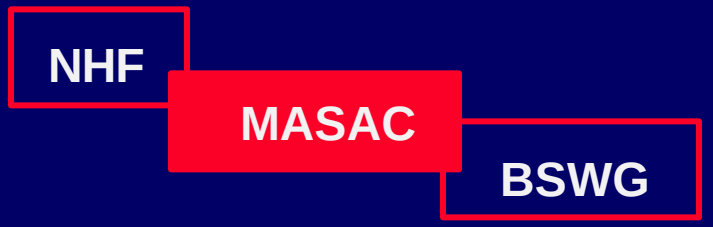


- *On record for encouraging US transition to recombinant FVIII / IX . . . , but*
- *Cogent arguments on behalf of the bleeding disorders community for preserving . . . and internationally harmonizing standards for plasma collection, processing and storage*
  - *. . . only option for RBD's such as FV / XI deficiencies is FFP*
  - *No recombinant vWf preparation is presently available . . .*

* Hoots: Letter to J. Goodman, August 2004

Plasma Standards

MASAC* (Continued)



- *Potential for exploiting under-utilized . . . plasma / plasma fractions to increase supply (lower the price) . . . for developing world*
- *. . . intermediate purity pathogen-inactivated FVIII . . . immune tolerance*
- *. . . implications of national standards for blood collection and processing on international needs . . . importing country o region*
- *. . . near catastrophic shortage of rFVIII . . . b / o availability of high quality PD FVIII, . . . no individual in the US experienced emergency bleeding for which there was no replacement therapy. This experience repeated in Europe. . .*

* Hoots: Letter to J. Goodman, August 200

Plasma Standards

BSWG / MASAC

NHF

MASAC

BSWG

Long Range Planning Document (2004)

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Key Goal of a Blood Safety Plan

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Availability of PD Products

- ***Lack of alternative choice for RBD's***
- ***Recombinant product back-up***
- ***Global needs / demand***
- ***Maintaining economic feasibility for other PD products (eg IVIG)***

Plasma Standards

World Federation of Hemophilia

n refuting the Shanbrom publication that "official recommendations o he WFH is to utilise recombinant products in the treatment of haemophilia.", Giangrande et al wrote:

. . . It is certainly not the policy of the WFH to recommend only recombinant products for the treatment of haemophilia. There is and will continue to be a global requirement for both plasma-derived and recombinant coagulation factor concentrates.

. . . Our aim is to ensure the availability of an adequate quantity of saf and effective products for the treatment of haemophilia in countries around the world . . . **(JTH, 2004; 2:1023)**

Plasma Standards

WFH / WHO Essential Drug List Application

Coagulation factors should be retained on the essential medicines list . . . because . . . ,:

- ***Major surgery difficult with BB products alone***
- ***Early therapy required to minimise morbidity / mortality not possible with BB products***
- ***Developing world . . . blood borne virus screening is inadequate***

Years of Rx	Venezuela			USA
	Lower (1 / 25,700)*	Mid (1 / 21,200)*	Upper (1 / 17,500)*	Mid (1,545,100)*
5	3.4#	4.2	5.0	0.16
30	19.0	22.5	26.6	0.99
60	34.3	39.9	46.0	2.0

*** estimated risk for HIV infected donation**

 # % risk of PWH being exposed to HIV-infected cryo

(WFH, April 2003)

Plasma Standards

WFH / WHO Essential Drug List Application

Requirement of factor concentrates

- Depends on economic capacity of the country, however
- Estimated minimum requirement (1 unit / head pop)

FVIII: 20,000 units / yr / pt for plasma-derived concentrates
FIX: 20,000 units / yr / pt for plasma-derived concentrates

Plasma Standards

Plasma Economics

s presented to BPAC (July 2004) by the PPTA:

Recent Developments

Consolidations / Divestitures

+

Plasma Collection / Fractionation Facility Closures

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Reduced Volume of Fractionated Plasma (Source + Recovered)

New Companies

+

Enhanced Technologies

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Potential for Higher Fractionation Yields

though no near term threat to plasma therapy availability

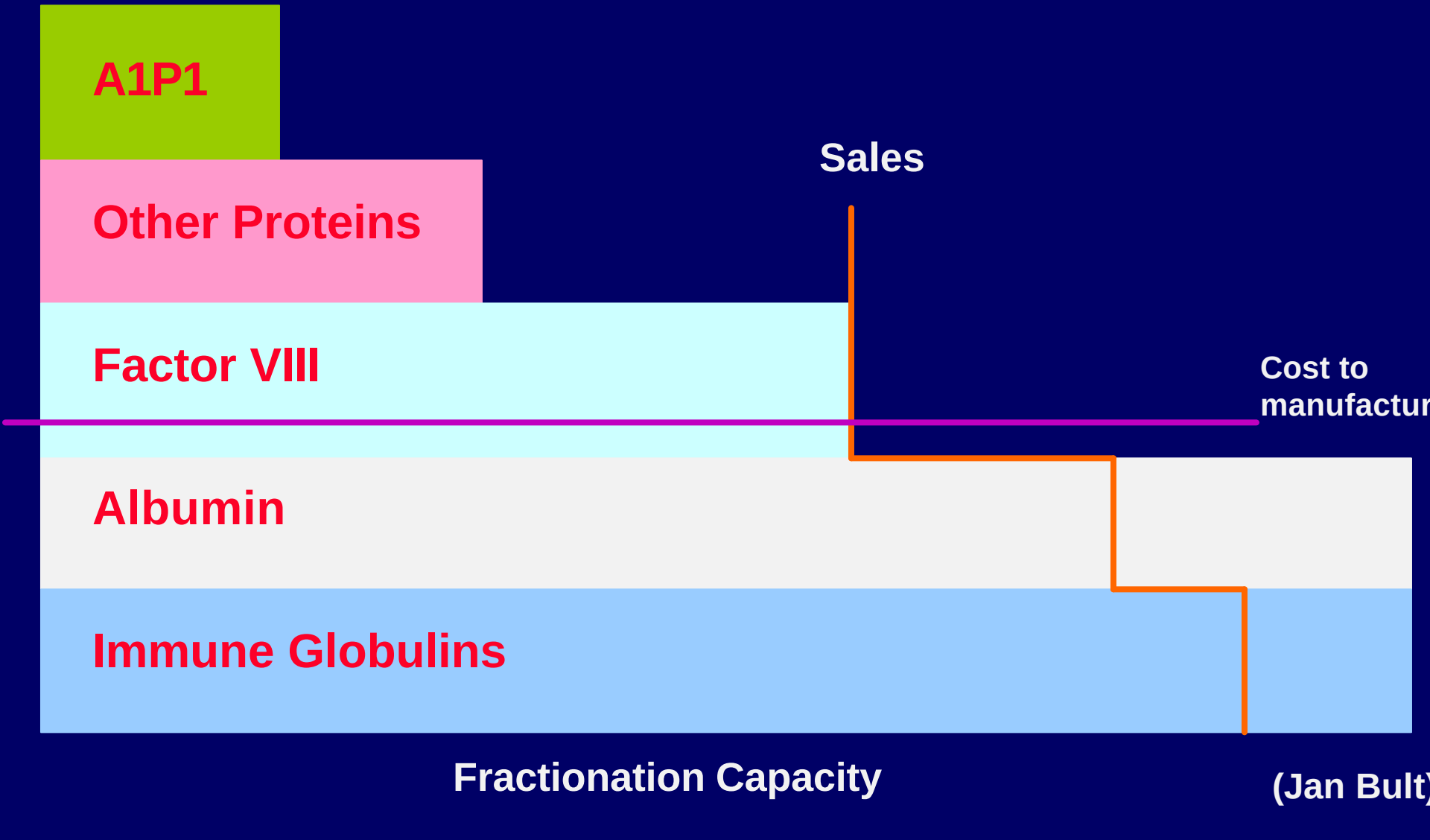
Plasma Standards

Maximizing Clotting Factor Yield

- Goal is not to discuss the technology of maximizing clotting factor yield. However, scientific data exists:
  - **A. Farrugia**
    - Today's presentation
  - **G. Rock**
    - Vox Sang 1979; 36:294 - 300
    - Thrombosis Research 1983; 29:521 - 535
    - NEJM 1984; 311:310 - 313

Plasma Standards

Plasma Economics



Plasma Standards

Achieving Maximum Factor Yield / Economic Sense (Cents)

. . . it is recognized by members of MASAC that insistence on the highest standards for plasma collection, processing, storage and shipping comes with a price tag . . .

. . . it may well be that capacity to use every plasma fraction . . . will prove to be cost effective

. . . higher up front costs may be . . . offset by mutually beneficial contracts for factor concentrates . . . to developing countries. . .

(Hoots, MASAC Letter to J. Goodman, August 200

Plasma Standards

Achieving Maximum Factor Yield / Economic Sense (Cents)

- **WFH: Application to WHO Essential Drug List**

Plasma-derived FVIII and FIX have been purchased at prices as low as US $0.10/unit, with a cost of US $0.20 – 0.30 being more commonly seen. These prices compare with the cost of producing cryoprecipitate in some countries which can be approximately US $0.20/unit.

Plasma Standards

ACBSA / August 2004

- **Recommendation to the DOH re the promotion of safe / effective therapy for RBD's: (August 2004)**
  - ***The committee recommends that DHHS promote the development of products to treat individuals with rare blood disorders including facilitating:***
    1. ***Obtaining additional licensed indications for already licensed products;***
    2. ***Approval of licensed indications in the US for Europea licensed products;***
    3. ***Developing new products***

Plasma Standards

Important Caveats

- Increased cost of maximizing clotting factor production cannot / should not be borne by others who currently benefit from plasma fractionation:
  - patients with immunodeficiency and / or autoimmune disease who currently benefit from immunoglobulin therapy
  - patients with a 1 AT deficiency

Plasma Standards

The Promise of Advocacy

- Coagulation Disorders Community will continue to address issues affecting the balance of product quality, affordability and profitability
  - Reimbursement
  - Harmonization of regulatory requirements for product licensure
  - Global access to care

Plasma Standards

Thanks and Good Luck!

- Applaud this meeting of national / international regulatory bodies, plasma collectors / fractionators and scientists
- Wish the discussants every success in the consensus building process